ESC European Society of Cardiology

European Heart Journal (2021) **42**, 2154–2169
doi:10.1093/eurheartj/ehaa1080

How low is safe? The frontier of very low (<30 mg/dL) LDL cholesterol

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Received 23 August 2020; revised 16 November 2020; editorial decision 16 December 2020; accepted 18 December 2020; online publish-ahead-of-print 19 January 2021

Low-density lipoprotein cholesterol (LDL-C) is a proven causative factor for developing atherosclerotic cardiovascular disease. Individuals with genetic conditions associated with lifelong very low LDL-C levels can be healthy. We now possess the pharmacological armamentarium (statins, ezetimibe, PCSK9 inhibitors) to reduce LDL-C to an unprecedented extent. Increasing numbers of patients are expected to achieve very low (<30 mg/dL) LDL-C. Cardiovascular event reduction increases log linearly in association with lowering LDL-C, without reaching any clear plateau even when very low LDL-C levels are achieved. It is still controversial whether lower LDL-C levels are associated with significant clinical adverse effects (e.g. new-onset diabetes mellitus or possibly haemorrhagic stroke) and long-term data are needed to address safety concerns. This review presents the familial conditions characterized by very low LDL-C, analyses trials with lipid-lowering agents where patients attained very low LDL-C, and summarizes the benefits and potential adverse effects associated with achieving very low LDL-C. Given the potential for cardiovascular benefit and short-term safe profile of very low LDL-C, it may be advantageous to attain such low levels in specific high-risk populations. Further studies are needed to compare the net clinical benefit of non-LDL-C-lowering interventions with very low LDL-C approaches, in addition to comparing the efficacy and safety of very low LDL-C levels vs. current recommended targets.

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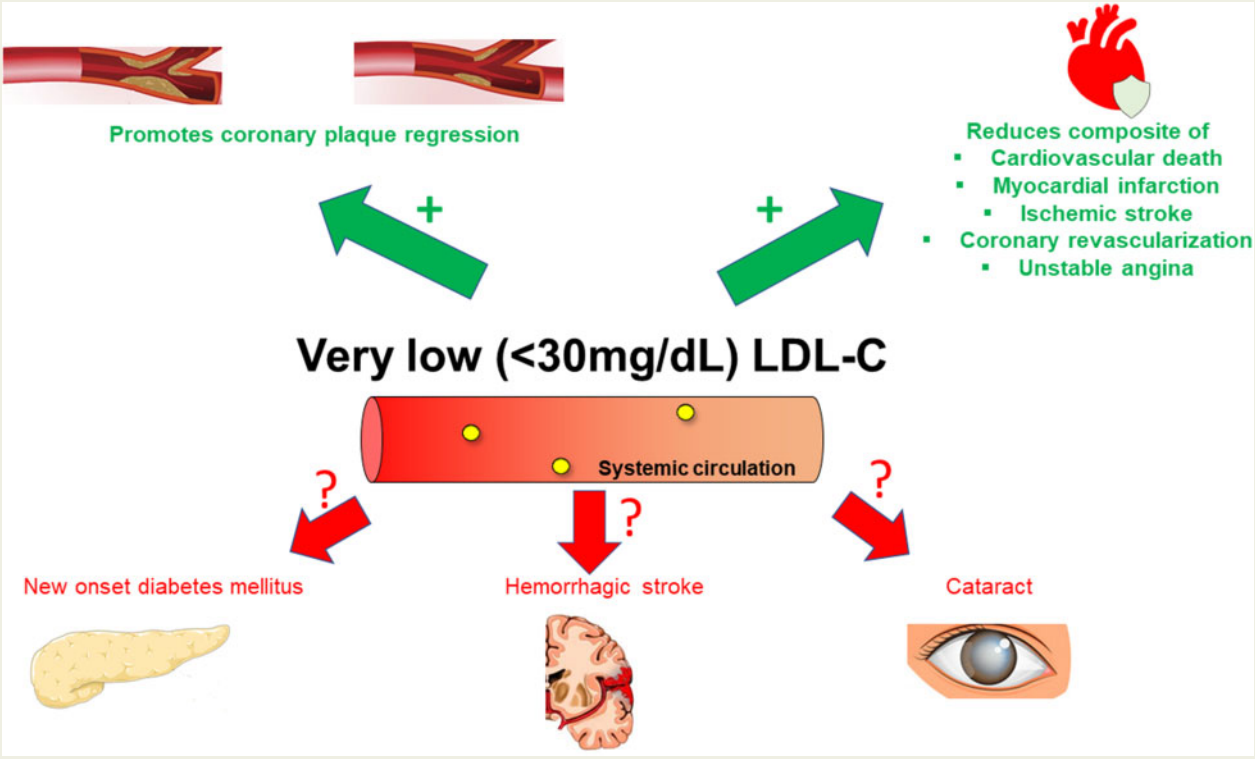
Graphical Abstract



Keywords Very low LDL-C levels • Cholesterol guidelines • PCSK9 inhibitors • Statins • Ezetimibe

Introduction

Coronary artery disease (CAD) is the leading cause of morbidity/mortality in the western world.[1] Serum low-density lipoprotein cholesterol (LDL-C) is a proven causative factor for developing CAD and a log linear correlation has been found between LDL-C and CAD risk.[2] Randomized controlled trials (RCTs) unequivocally show that lowering serum LDL-C is associated with a significant reduction in major adverse cardiovascular events, which include a composite of cardiovascular death, myocardial infarction (MI), stroke, coronary revascularization, and unstable angina.[3–7]

Very low (<30 mg/dL) LDL-C can be found in patients with genetic conditions characterized by hypocholesterolaemia, in patients undergoing pharmacological treatment with lipid-lowering agents and transiently post LDL apheresis. Loss-of-function mutations in Proprotein Convertase Subtilisin/Kexin 9 gene (*PCSK9*), familial hypobetalipoproteinemia, abetalipoproteinemia, familial combined hypolipidaemia, chylomicron retention disease, and Smith–Lemli–Opitz syndrome are genetic conditions characterized by congenital, lifelong, very low LDL-C.[8,9] These conditions could be used as proxies for understanding the benefits and potential side effects of living with very low LDL-C levels in the long term. Finally, in patients undergoing LDL apheresis, very low LDL-C levels have been transiently observed post-apheresis, without any associated side effect.[10]

In recent years, potent LDL-C-lowering medications have emerged (high-intensity statins, statin/ezetimibe combination, PCSK9 inhibitors including evolocumab, and alirocumab). These agents reduce LDL-C to an unprecedented extent and have relatively minimal side effects at short to intermediate follow-up.[3–7,11–13] Cardiovascular benefit continues to increase with lowering LDL-C even when very low LDL-C is attained.[14–16] However, it is still unclear whether very low LDL-C *per se* is associated with significant clinical adverse effects. Existing literature has been controversial; few sub-studies of patients attaining very low LDL-C indicate a higher incidence of side effects,[17,18] whereas other sub-studies report no adverse effects.[15,16,19] As a growing number of patients taking potent lipid-lowering medications achieve very low (<30 mg/dL) LDL-C, it is of paramount importance to evaluate the safety of very low LDL-C levels in the long-term.

In light of recent data with favourable outcomes among patients attaining low LDL-C without proven concern for side effects, recent European and American Cholesterol Management guidelines have adopted a more aggressive lipid-lowering approach in high-risk patients.

The 2016 European Society of Cardiology (ESC) CVD prevention guidelines recommended an LDL-C goal of <70 mg/dL or at least a 50% LDL-C reduction in high-risk patients with baseline levels 70–135 mg/dL.[20] Given evidence of cardiovascular benefit with even lower LDL-C, the 2019 ESC/EAS Cholesterol Guidelines recommended lowering LDL-C to <55 mg/dL in very high-risk patients for both primary and secondary prevention (Class I recommendation) and to <40 mg/dL in patients experiencing a second vascular event within 2 years (Class IIb).[21] The 2019 ESC/EAS guideline defines very high-risk patients as those with documented atherosclerotic cardiovascular disease (ASCVD) (clinical or on imaging), with diabetes (with associated target organ disease, at least three major risk factors, or early onset of T1DM >20 years), with advanced chronic kidney disease not on haemodialysis, or with familial hypercholesterolaemia plus a major risk factor.

In contrast, the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) Cholesterol Guidelines did not recommend a specific minimum LDL-C target. Instead, guidelines recommended that preferred statin intensity and percent LDL-C reduction goal should be based upon patient's cardiovascular risk.[22] The 2018 AHA/ACC/Multi-society guidelines, which incorporated data from three new RCTs (IMPROVE-IT, FOURIER, ODYSSEY OUTCOMES) addressed the need for a more aggressive approach of LDL-C lowering in very high-risk ASCVD patients, recommending achieving at least a 50% reduction in LDL-C and a 70 mg/dL LDL-C threshold to consider further LDL-C lowering with ezetimibe, and if needed by a PCSK9 inhibitor.[23]

This review presents the familial conditions characterized by very low LDL-C, analyses lipid-lowering trials where patients attained very low LDL-C, and summarizes the benefits and potential adverse effects associated with achieving very low LDL-C. Several reviews analysing the mechanisms and safety of achieving very low LDL-C levels have been published in the past few years.[24,25] However, given management of hypercholesterolaemia continues to drastically evolve, an up-to-date comprehensive review is needed. Of note, there is not a universal definition of very low LDL-C and there are different methods to determine the LDL-C value. For the purpose of this review, we define very low serum LDL-C as below 30 mg/dL.

Different methods of measuring LDL-C

In the lower ranges of LDL-C, attention to measurement is crucial. There are several available methods for measuring LDL-C

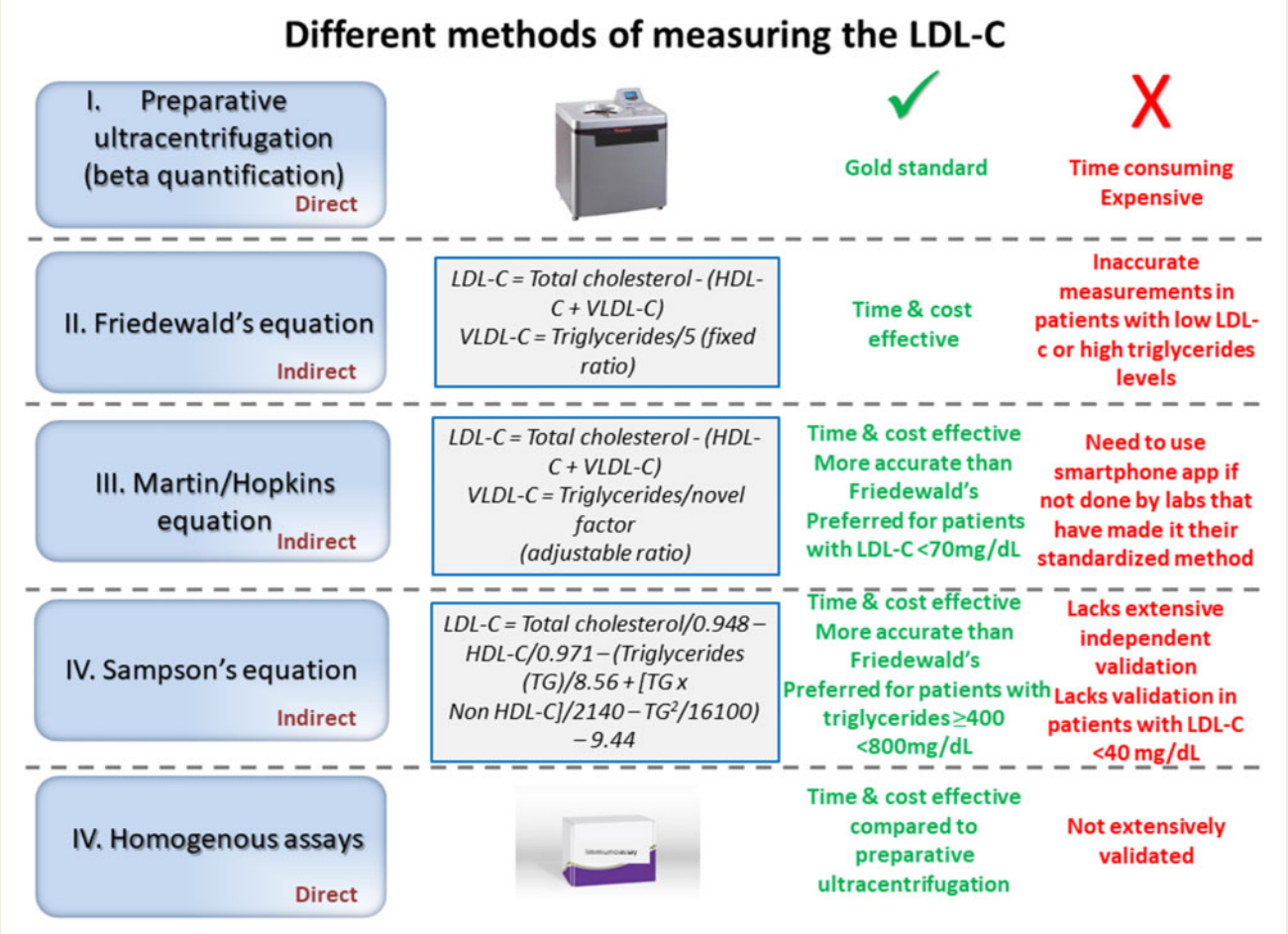


Figure 1 Different methods of measuring the LDL-C. LDL-C can be measured using various techniques. As recent cholesterol guidelines recommend achieving lower LDL-C, it is crucial to use methods that measure LDL-C accurately in low LDL-C ranges.

(*Figure 1*).[26,27] In routine clinical practice, LDL-C is not measured directly but is calculated based on the measured total cholesterol, HDL-cholesterol and triglycerides using the Friedewald equation. However, it has been shown that Friedewald-calculated LDL-C can be significantly underestimated in patients with low LDL-C (<70 mg/dL) or with elevated triglycerides.[28] Direct LDL-C measurement with preparative ultracentrifugation (beta quantification) is the most accurate approach in these patients (gold standard), but it is costly, time consuming, and therefore, not often performed.[28] Both the FOURIER and ODYSSEY OUTCOMES trials used beta quantification for patients with very low LDL-C levels to increase accuracy.[6,7]

The Martin/Hopkins method is a novel, practical, indirect LDL-C calculation equation that is cost and time effective.[29] A *post hoc* analysis of the FOURIER trial showed that, when compared to the ultracentrifugation standard, 13.3% of Friedewald calculated values differed by >10 mg/dL, as contrasted with only 2.6% by the Martin/Hopkins method.[30] In a nationally representative sample, a hospital laboratory, and a reference laboratory, approximately one-fifth of individuals with Friedewald-estimated LDL-C < 70 mg/dL have a value of ≥70 mg/dL using the Martin/Hopkins LDL-C equation.[31] These individuals usually have significantly higher non-HDL-C and apoB concentrations, conferring an increased risk for cardiovascular disease.[31] Recently, Sampson *et al.*[32] have reported a new method for improving LDL-C calculation. LDL-C values derived by Sampson's method compare favourably with results obtained by preparative ultracentrifugation, long considered a 'gold standard' for LDL-C measurement, even in patients with very high triglyceride levels. Overall, Sampson's equation extends the accuracy of LDL-C calculation to individuals with triglyceride values up to 800 mg/dL, whereas Martin's equation significantly improves LDL-C estimation in patients with low LDL-C levels (<70 mg/dL).[33]

Finally, direct beta quantification should not be confused with commercially available homogenous assays that use proprietary chemical-based methods to measure LDL-C directly and are not necessarily reliable or standardized.[34–36]

Understanding the importance of more accurate measurement is essential in any discussion of LDL-C levels <70 mg/dL. High-risk patients with the LDL-C levels of 50–70 mg/dL may be considered well managed based upon the Friedewald-calculated LDL-C; however, they may, in fact, benefit from additional LDL-C lowering if a more accurate method such as the Martin/Hopkins method was used. Given evidence of the Martin/Hopkins method's improved accuracy, the 2018 AHA/ACC/Multi-society Cholesterol Guideline supports its use in persons with low LDL-C levels[23] and it is possible that future guidelines will consider the broader use of this method.

Of note, most LDL-C determining methods, including ultracentrifugation and Friedewald-calculated LDL-C, incorrectly count the cholesterol present in Lp(a) particles as 'LDL-C', thus overestimating LDL-C levels.[37] Lp(a)-corrected LDL-C can be estimated with the Dahlen modification, which assumes that 30% of Lp(a) weight consists of cholesterol: LDL-C - [Lp(a) × 0.30].[38,39]

Finally, plasma LDL-C is a measure of cholesterol mass carried by LDL particles (LDL-p) and therefore only an estimate of circulating LDL-p. In most clinical settings, measured LDL-C mirrors LDL-p values. However, there are conditions (e.g. hypertriglyceridaemia, metabolic syndrome) where patients may have normal LDL-C, while having lower cholesterol mass per LDL particle and larger LDL-p numbers, being thus in higher cardiovascular risk than expected on their LDL-C measurements.[37] Even though LDL-p is the most abundant apoB-containing circulating lipoprotein and the lipoprotein for which we have clear evidence of its atherogenicity, other ApoB lipoproteins (VLDL, ILDL) may also be atherogenic. A Mendelian randomization study showed that TG-lowering lipoprotein lipase variants and LDL-C-lowering LDL receptor variants had the same impact on ASCVD risk per unit change of ApoB, suggesting that all ApoB-containing lipoproteins have the same effect on the risk of cardiac heart disease and that the clinical benefit of LDL-C and triglyceride-lowering treatments may be proportional to the absolute difference in ApoB.[40] In a meta-analysis, the mean risk reduction per SD decrease was higher for apoB [24%; 95% confidence interval (CI), 19–29%] compared to 20% (16–24%) for LDL-C and 20% (15–25%) for non-HDL-C across seven major statin trials.[41] ApoB measurement is an easy, fully automated, standardized, fasting-independent test that can accurately detect the numbers of plasma atherogenic lipoproteins as well as elevated LDL-p often missed with LDL-C alone. Per 2019 ESC/EAS guidelines, it should be considered as a complementary marker to LDL-C for ASCVD risk calculation (especially in people with high triglyceride levels, diabetes mellitus, obesity, metabolic syndrome, or very low LDL-C levels) or as an alternative to LDL-C, as the primary measurement for screening, diagnosis, and management.[21]

Genetic conditions associated with very low LDL-C

Six genetic conditions (*PCSK9* loss-of-function mutations, abetalipoproteinemia, familial hypobetalipoproteinemia, familial combined hypolipidemia, chylomicron retention disease, and Smith–Lemli–Opitz syndrome) are associated with very low LDL-C levels (*Figure 2*). Healthy human neonates have baseline low LDL-C (30–70 mg/dL)[42] and a percentage of healthy neonates are found with LDL-C levels even <30 mg/dL.[43,44]

PCSK9 is a serine protease that tightly binds to the LDL receptor (LDL-R) and subsequently chaperones the LDL-R to the intracellular degradative organelles for dismantling.[45] Individuals with *PCSK9* loss-of-function mutations have increased numbers of LDL-R on the surface of their hepatocytes that promotes robust LDL-C clearance from the circulation leading to lifelong reduction in LDL-C. Such individuals are healthy, do not have any apparent secondary morbidities, and experience a significant reduction in cardiovascular events over long-term follow-up.[9,46,47]

Although PCSK9 is expressed in the brain, liver, intestine and kidneys, a compound heterozygote for loss-of-function *PCSK9* mutations with 14 mg/dL serum LDL-C was found to be healthy, fertile and without any neurocognitive impairment.[48] One study showed that PCSK9 variants have an LDL-C-dependent risk for developing diabetes; for each 10 mg/dL LDL-C decrease, there is an 11% increase in diabetes risk.[46] On the contrary, another study did not support any correlation between low LDL-C and type 2 diabetes in individuals with the most frequent PCSK9 loss-of-function variant.[49]

Abetalipoproteinemia is a rare autosomal recessive disorder resulting from mutation of the microsomal triglyceride transfer protein (MTP), which is essential for assembling all apoB lipoproteins.

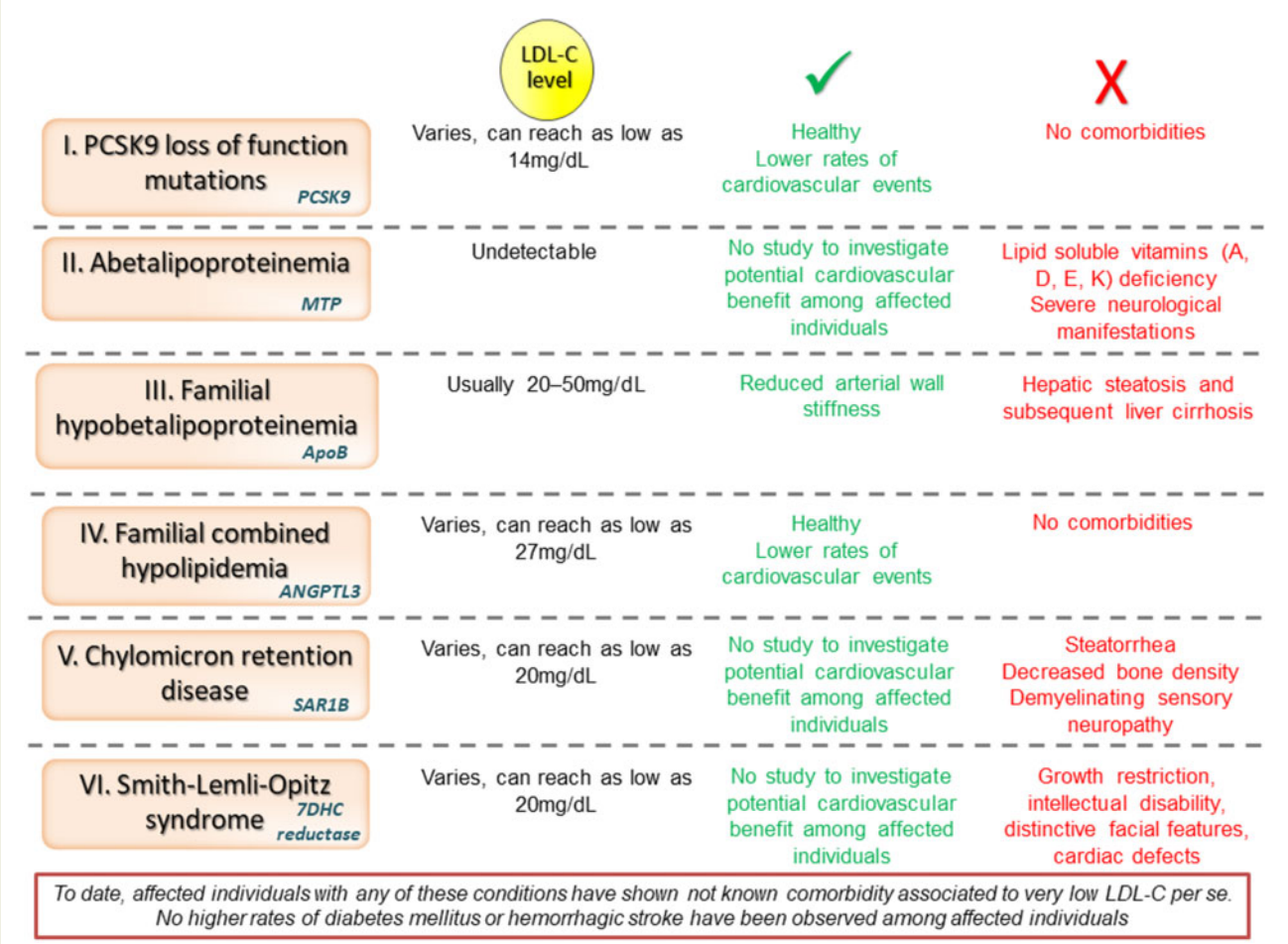


Figure 2 Genetic conditions associated with very low LDL-C. Thus far, six different genetic conditions associated with very low (<30 mg/dL) LDL-C have been identified. Analysis of individuals living with these conditions may help in better understanding potential benefits and side effects of living with very low LDL-C long term.

Abetalipoproteinemia is characterized by the absence of serum apoB-containing lipoproteins, undetectable LDL-C, in addition to deficiency of lipid soluble vitamins (A, D, E, K).[50] Affected individuals present with severe neurological manifestations including retinal degeneration, spinocerebellar ataxia, peripheral neuropathy, and posterior column neuropathy, as well as steatorrhoea, hepatic steatosis, myositis, and acanthocytosis. The demyelination that leads to aforementioned neurological presentation seems to be associated with vitamin E deficiency and not related to absence of LDL-C.[51] Lifelong supplementation with high-dose vitamin E appears to halt further neurological degeneration.[52] Other manifestations associated with the condition (myalgias/myositis) are also LDL-C independent as they improve with high doses of fat-soluble vitamins[52] and, thus far, absent serum LDL-C has not been identified as a cause of any specific adverse consequences in abetalipoproteinemia patients.[50]

Familial hypobetalipoproteinemia (FHBL) is an autosomal dominant disorder caused by mutations of the apoB gene, which results in decreased lipidation and secretion of apoB-containing lipoproteins from hepatocytes to the circulation.[53] FHBL is associated with LDL-C typically between 20 and 50 mg/dL, although affected individuals have been found with LDL-C as low as 17 mg/dL.[53] Heterozygotes with FHBL are usually asymptomatic but can develop hepatic steatosis and subsequent liver cirrhosis. Hepatic steatosis is most likely secondary to the accumulation of apoB-containing lipoproteins in the hepatocytes but should be further investigated if hepatosteatosis is also related to decreased hepatocellular ApoB lipoproteins production and subsequently very low LDL-C.[54] Eighty-two patients with FHBL were found to have reduced arterial wall stiffness, although this study did not evaluate whether the observed reduced arterial stiffness was directly correlated with lower LDL-C *per se*.[54]

Familial combined hypolipidaemia (FHBL2) and chylomicron retention disease (CRD) are very rare genetic conditions caused by mutations in Angiopoietin-like 3 (ANGPTL3) and SAR1B proteins, respectively. Individuals with FHBL2 are found to have a significant reduction of all apoB- and apoAI-containing lipoproteins with some homozygous carriers having LDL-C as low as 27 mg/dL.[55] Two

studies of FHBL2 patients showed no diabetes or cardiovascular disease among a small sample of homozygous carriers.[55,56] Studies have also demonstrated that individuals with ANGPTL3 loss-of-function mutations have decreased odds of developing ASCVD.[56,57] CRD is characterized by hypocholesterolaemia in the presence of normal triglycerides.[58] Affected individuals with CRD present with steatorrhoea, decreased bone density, demyelinating sensory neuropathy and abnormal visual evoked potentials; all aforementioned signs/symptoms are in the setting of fat and fat-soluble vitamin malabsorption and are not associated with the low LDL-C.[58]

Smith–Lemli–Opitz syndrome (SLOS) is a congenital syndrome caused by the deficiency of 7-dehydrocholesterol (7-DHC) reductase enzyme, which is necessary for cholesterol synthesis.[59,60] The clinical spectrum and severity of presentation varies; patients with SLOS can present with prenatal and postnatal growth restriction, moderate-to-severe intellectual disability, distinctive facial features, cardiac defects, underdeveloped external genitalia in males and 2–3 syndactyly of the toes.[60] Laboratory findings are significant for elevated 7-DHC and usually low serum total cholesterol and LDL-C (some patients have even LDL-C < 30 mg/dL), albeit many patients will have normal cholesterol and LDL-C levels.[61] It is unclear if syndrome's pathophysiology is secondary to decreased cholesterol synthesis (e.g. reduced local de novo cholesterol production in the central nervous system), or to lower cholesterol levels or to toxic accumulation of the prodrome 7-DHC.

Sub-studies/secondary analyses of patients achieving very low LDL-C

HMG-CoA reductase inhibitors (statins), NPC1L1 inhibitor (ezetimibe), and PCSK9 inhibitors (evolocumab, alirocumab) are lipid-lowering drugs that significantly reduce LDL-C and the incidence of cardiovascular events.[62] In several trials (JUPITER, PROVE-IT TIMI-22, IMPROVE-IT, FOURIER, ODYSSEY trials) with lipid-lowering agents (high-intensity statin, statin/ezetimibe combination, statin/PCSK9 inhibitor combination, PCSK9 monotherapy) ~10–25% of patients in the treatment groups achieved very low (<30 mg/dL) LDL-C.[3,4,6,7,63] The combination of a PCSK9 inhibitor with a statin ± ezetimibe results in the greatest LDL-C reduction.

Published sub-studies of the aforementioned trials focused specifically on patients achieving very low LDL-C values, analysing possible benefits and adverse effects between treatment groups based on attained LDL-C levels (*Table 1*).[15–19] The largest reported experience with LDL-C < 30 mg/dL is with evolocumab in the FOURIER trial.[16] In that trial, the median LDL-C at 4 weeks was 19.4 mg/dL (<0.5 mmol/L) and trended slightly higher over the next 168 weeks. The longest exposure, though, was seen in IMPROVE-IT trial of over 6 years.[15]

The profile of patients attaining very low LDL-C is most frequently characterized by lower baseline LDL-C and Lp(a) levels, higher baseline triglycerides, male gender, older age, non-smokers, history of diabetes, higher haemoglobin A1c, and higher dose of lipid-lowering medications.[15,16,18,19]

Benefits of achieving very low LDL-C

Lower LDL-C appears to be atheroprotective and reduces the incidence of cardiovascular events. However, it is important to assess if cardiovascular benefit extends below 30 mg/dL. The GLAGOV study[64] used intracoronary intravascular ultrasound to evaluate the effect of evolocumab on coronary atheroma volume when administered to statin-treated patients. Patients on evolocumab had lower LDL-C (36.6 vs. 93.0 mg/dL; difference -56.5 mg/dL [95% CI, -59.7 to -53.4]; $P < 0.001$), slightly decreased percent atheroma volume (PAV) [0.95% decrease vs. 0.05% increase, difference -1.0% (95% CI, -1.8% to -0.64%); $P < 0.001$], lower normalized total atheroma volume (TAV) [5.8 mm^3 decrease vs. 0.9 mm^3 decrease, difference -4.9 mm^3 (95% CI, -7.3 to -2.5); $P < 0.001$], and modest atherosclerotic plaques regression [64.3% vs. 47.3%; difference 17.0% (95% CI, 10.4–23.6%); $P < 0.001$ for PAV and 61.5% vs. 48.9%; difference 12.5% (95% CI, 5.9–19.2%); $P < 0.001$ for TAV]. A linear relationship between achieved LDL-C and percent atheroma volume progression was found ranging from 110 mg/dL to as low as 20 mg/dL.[64]

Sub-studies focused on patients achieving very low LDL-C have demonstrated a statistically significant reduction in the composite of cardiovascular death, myocardial infarction, ischaemic stroke, coronary revascularization, and unstable angina compared to patients with LDL-C values >30 mg/dL.[15,16,19] It appears that cardiovascular clinical benefit is log linearly dependent on LDL-C, increases monotonically with lower LDL-C, is conferred even to patients who start a lipid-lowering agent with a baseline LDL-C < 70 mg/dL, and is similar whether achieved by any combination of a statin, ezetimibe, and PCSK9 inhibitor.[15,16,65] The FOURIER trial did not show a cardiovascular benefit plateau, even for LDL-C levels as low as 10 mg/dL.[16]

In a prespecified analysis of ODYSSEY OUTCOMES trial in patients eligible for ≥3 years follow-up, alirocumab reduced all-cause death [hazard ratio (HR), 0.78; 95% CI, 0.65–0.94; $P = 0.01$].[66] A *post hoc* spline analysis from the same trial showed that in the alirocumab group all-cause mortality declines with lower achieved LDL-C levels, down to an LDL-C level of ~30 mg/dL (adjusted *P*-value for model = 0.017 for linear trend).[66] Whether all-cause mortality continues to decrease for LDL-C below 30 mg/dL is still unclear.

A *post hoc* analysis of FOURIER showed that PCSK9 inhibition reduced venous thromboembolism (VTE) events by 46% (HR, 0.54; 95% CI, 0.33–0.88; $P = 0.014$) beyond 1 year,[67] a meta-analysis of FOURIER and ODYSSEY OUTCOMES demonstrated a 31% relative decrease in VTE with PCSK9 inhibition (HR, 0.69; 95% CI, 0.53–0.90; $P = 0.007$)[67] and a prespecified analysis of Odyssey OUTCOMES showed a nonsignificant trend of fewer VTE events (HR, 0.67; 95% CI, 0.44–1.01; $P = 0.06$) in the treatment group.[68] Even though none of the studies find any correlation between VTE events rate and baseline LDL-C or magnitude of LDL-C reduction, a dedicated RCT investigating the possible effect of lowering LDL-C [or other lipoproteins such as Lp(a)] on lowering VTE events might be warranted. Similarly, evolocumab was found to reduce aortic stenosis events (HR of 0.48; 95% CI, 0.25–0.93) after the first year of treatment in an exploratory analysis of the FOURIER trial; however, there was not found any significant correlation between events and baseline LDL-C levels and further investigation is also needed.[69]

Table 1 Secondary analyses/sub-studies of patient groups achieving very low (<30 mg/dL) LDL cholesterol levels

Secondary analysis ref	Pharmaceutical agent	Trial	LDL-C cut-off level (# subjects with very low LDL-C)	Median follow-up (years)	Benefits	Adverse effects
Wiviott *et al.*[19]	Atorvastatin 80 mg	PROVE IT-TIMI 22	<40 mg/dL ($n = 193$)	2 (mean)	Fewer major cardiac events (death, MI, stroke, recurrent ischaemia, revascularization) observed in <40 mg/dL group compared to >40 mg/dL	No association with any specific side effect
Everett *et al.*[17]	Rosuvastatin 20 mg	JUPITER	<30 mg/dL ($n = 767$)	1.9	No analysis to investigate association with the rate of CV events was performed	Higher risk of physician-reported type 2 diabetes, haematuria, hepatobiliary disorders, and insomnia
Giugliano *et al.*[15]	Ezetimibe/simvastatin	IMPROVE-IT	<30 mg/dL ($n = 971$)	6	Significantly lower risk of cardiovascular death, major coronary events, or stroke in patients with LDL-C < 30 vs. ≥70 mg/dL	No association with any specific side effect
Giugliano *et al.*[16]	Evolocumab	FOURIER	<20 mg/dL ($n = 2669$) 20–50 mg/dL ($n = 8003$)	2.16	Strong relationship between achieved LDL cholesterol down to concentrations 8 mg/dL and a progressive reduction in major cardiovascular outcomes	No association with any specific side effect
Robinson *et al.*[18]	Alirocumab	Pooled data from 14 alirocumab trials	≤25 mg/dL ($n = 839$) ≤15 mg/dL ($n = 314$)	2 (longest trial)	Analysis comparing CV events between LDL-C ≤ 25 mg/dL and LDL-C > 25 mg/dL groups was not performed due to insufficient numbers in the former group	Higher rate of cataracts (2.6% vs. 0.8%) in patients with LDL-C ≤ 25 mg/dL vs. >25 mg/dL

Safety and tolerability of achieving very low LDL-C

Nervous system

Given that cholesterol is a major membrane component of brain cells, there were initial concerns about the effect of intense LDL-C lowering on neurocognitive function. The OSLER study showed that patients receiving evolocumab/statin treatment reported statistically more neurocognitive events (delirium, cognitive and attention disorders, dementia and amnestic conditions, disturbances in thinking and perception, and mental impairment disorders) compared to patients on statin monotherapy (0.9% vs. 0.3%); the risk of neurocognitive events, though, did not significantly vary between patients achieving very low LDL-C and patients who did not.[70]

EBBINGHAUS, a sub-study of FOURIER, investigated the effect of evolocumab on neurocognitive function and found no difference in cognitive function between the evolocumab/statin vs. statin-only groups at a median of 19 months. The primary endpoint of spatial working memory strategy index of executive function was -0.21 ± 2.62 in the evolocumab vs. -0.29 ± 2.81 in the placebo group ($P < 0.001$ for noninferiority). Also, there was no difference between subgroups stratified based on attained LDL-C (including patients in the <25-mg/dL subgroup).[71] However, given EBBINGHAUS study's limitations including short follow-up (a median follow-up of 19 months), enrolment of relatively young patients (mean age of 63 years old), and exclusion of patients with known dementia or mild cognitive impairment, further long-term monitoring for possible memory/cognition worsening in high-risk patients is necessary. Additional data from PCSK9 inhibitor trials and sub-studies with

participants achieving very low LDL-C have not shown any correlation between marked LDL-C reduction and neurocognitive impairment.[6,7,15,16,18] It is noteworthy that brain cholesterol regulation is primarily dependent upon local *de novo* cholesterol synthesis in the brain rather than levels of circulating plasma cholesterol.[72] Therefore, lipid-lowering agents, which decrease peripheral LDL-C, are unlikely to have significant impact on brain cholesterol levels.

Several studies have reported a possible correlation between lower LDL-C and haemorrhagic stroke incidence or associated mortality. The SPARCL study showed that patients with prior stroke treated with atorvastatin 80 mg had a higher incidence of intracranial haemorrhage compared to placebo (55[2.3%] vs. 33[1.4%]; $P = 0.02$).[73] In addition, a CTT meta-analysis showed evidence of a small increased rate of haemorrhagic stroke among patients treated with statins (5–10 haemorrhagic strokes per 10 000 patients in whom LDL-C is reduced by 39–77 mg/dL for 5 years); the excess risk, though, was small and much less frequent than the reduction in ischaemic strokes and was not associated with an increase in mortality.[74]

One small study of 88 consecutive patients found that those with LDL-C < 70 mg/dL had higher 90-day mortality following an episode of intracerebral haemorrhage compared to patients with >70 mg/dL.[75] Low LDL-C was correlated with elevated risk of death due to intraparenchymal haemorrhage in a Japanese population.[76] Patients with LDL-C ≥ 70 mg/dL had a lower intracerebral haemorrhage incidence compared to patients with LDL-C of 50–69 and <50 mg/dL, respectively, in a nine year follow-up cohort study {adjusted hazard ratio 1.65 (95% CI 1.32–2.05) for LDL-C 50–69 mg/dL and 2.69 (95% CI 2.03–3.57) for LDL-C < 50 mg/dL}.[77] In a prospective cohort study among women, after multivariable adjustment, women with LDL-C < 70 mg/dL had 2.17 times the risk (95% CI; 1.05, 4.48) of a haemorrhagic stroke compared to women with LDL-C 100–129.9 mg/dL over a mean of 19.3 years follow-up.[78] Although results were not significant due to limited statistical power, one meta-analysis showed that haemorrhagic stroke incidence was somewhat higher among patients with LDL-C < 50 mg/dL compared to patients with moderately low levels,[79] and another meta-analysis found that lower LDL-C concentration was associated with a higher risk of haemorrhagic stroke.[80]

Other meta-analyses, however, did not find any association between haemorrhagic stroke and statin use or lower LDL-C.[81–83] An analysis of ODYSSEY OUTCOMES results showed that alirocumab significantly decreased the risk of any stroke and the risk of ischaemic stroke without increasing the risk of haemorrhagic stroke [HR, 0.83; 95% CI, 0.42–1.65] in patients with recent acute coronary syndrome and persistent dyslipidaemia despite intensive statin therapy.[84] Importantly, the same analysis found that there was no adverse association between incidence of haemorrhagic stroke and lower attained LDL-C even in patients achieving LDL-C < 25 mg/dL, over a median of 2.8 years follow-up.[84] A recently published large cohort study found that initiation of statin in patients with prior stroke (either haemorrhagic or ischaemic) did not increase the risk of intracerebral haemorrhage in 10 years follow-up.[85] A trial of French/Korean population showed that post ischaemic stroke patients with an LDL-C goal target <70 mg/dL had no significant increase in haemorrhagic stroke compared to patients in the 90–110-mg/dL group (HR, 1.38; 95% CI, 0.68–2.82) over a median follow-up of 3.5 years.[86] Data from people with congenital low LDL-C, sub-studies of patients with very low LDL-C and prospective studies involving thousands of patients attaining low LDL-C have shown no correlation between lower LDL-C and haemorrhagic stroke.[5–7,15,19,50,84,87–90]

Given conflicting literature data, it is still unclear if lower LDL-C levels are associated with higher incidence of haemorrhagic stroke. Also, given haemorrhagic stroke risk may differ among the use of different lipid-lowering agents (e.g. statins vs. PCSK9 inhibitors) or among race (Asian population studies appear more consistent on an association between lower LDL-C and higher haemorrhagic stroke rates),[76,77] an individualized, lipid-lowering approach should be considered based on each patient's risk.

A secondary analysis of JUPITER found increased incidence of insomnia in patients with LDL-C < 30 mg/dL compared to patients with ≥30 mg/dL.[17] However, other sub-studies with patient groups achieving very low LDL-C have not supported higher rates of insomnia.[15,18]

Large prospective cohort studies have found an association of lower LDL-C levels and increased Parkinson's disease incidence,[91,92] including a cohort study with further Mendelian randomization.[93] Long-term surveillance for Parkinson's disease in patients achieving very low LDL-C might be reasonable.

Endocrine system

Statin use is associated with a modest increased incidence of new-onset diabetes.[94,95] A meta-analysis of RCTs with statins including 91 140 participants showed that treatment of 255 patients with statins for 4 years resulted in the reduction in 5.4 major coronary events and 1 extra case of diabetes.[94] Overall, cardiovascular benefit outweighs the increased risk for new-onset diabetes mellitus and clinical practice in patients with multiple cardiovascular risk factors or existing cardiovascular disease should not be modified.[94,95] Also, studies showed that statins moderately increase fasting plasma glucose (FPG)/HbA1c soon after statins initiation, but since the FPG/HbA1c values then remain stable through time, it is mostly the patients with pre-diabetes and elevated body mass index who are more prone to develop statin-induced new-onset diabetes.[96,97] Furthermore, although data from a mendelian randomization study support that variants in PCSK9 and HMGCR genes were correlated with higher diabetes risk per unit decrease in LDL-C,[46] so far, patient studies have not shown any effect of PCSK9 inhibitors on increasing the FPG or new-onset diabetes incidence. Whether new-onset diabetes incidence is increased among patients achieving very low serum LDL-C is still unclear. It is also uncertain whether new-onset diabetes is purely a statin-associated side effect and may not be associated with lowering LDL-C *per se* or with other lipid-lowering agents use.

In a pooled analysis of data from five statin trials, intensive-dose statin therapy was associated with a higher risk of new-onset diabetes compared with moderate dose therapy (odds ratio 1.12, 95% CI, 1.04–1.22).[98] A cross-sectional study found that individuals not on statin treatment with LDL-C < 60 mg/dL had a higher rate of type 2 diabetes compared to individuals with LDL-C levels between 90 and 130 mg/dL.[99] A sub-study of JUPITER demonstrated that rosuvastatin-treated patients attaining LDL-C < 30 mg/dL had increased risk for developing new-onset diabetes compared to those with LDL-C ≥ 30 mg/dL.[17] However, this was not related to the

degree of LDL-C lowering as there was no increased risk of diabetes in patients with large (≥70) percent reductions in LDL-C.[17]

The FOURIER and ODYSSEY OUTCOMES trials, with a combined pool of 46,488 patients (many of whom achieved very low LDL-C), did not show any significant increase in new-onset diabetes rates in patients on PCSK9 inhibitor/statin combination (FOURIER; hazard ratio, 1.05; 95% CI, 0.94–1.17. ODYSSEY OUTCOMES; 9.6% in alirocumab group vs. 10.1% in placebo group).[6,7] A pre-specified analysis of FOURIER, designed to investigate the effect of evolocumab on glycaemia and risk of developing diabetes showed that evolocumab neither increased the risk of new-onset diabetes in patients without diabetes or pre-diabetes at baseline [(hazard ratio 1.05, 95% CI 0.94–1.17) and (hazard ratio 1.00, 95% CI 0.89–1.13), respectively], nor did it worsen glycaemia over a median of 2.2 years of follow-up.[100] Similarly, a prespecified analysis of ODYSSEY OUTCOMES showed that treatment with alirocumab targeting an LDL-C of 25–50 mg/dL did not increase new-onset diabetes rates in patients with pre-diabetes or normoglycaemia at baseline when compared to placebo group (HR 1.00; 95% CI 0.89–1.11) over a 2.8 median follow-up.[101] The same study demonstrated that in the alirocumab treatment group, targeting an LDL-C of 25–50 mg/dL, resulted in twice the absolute reduction in cardiovascular events among patients with diabetes (2.3%, 95% CI 0.4–4.2) compared to those without diabetes (1.2%, 95% CI 0.0–2.4), respectively.[101]

A meta-analysis of RCTs with statins and statin/PCSK9 inhibitors as interventions in 163,688 nondiabetic patients investigated the association of intense vs. less intense lipid-lowering therapy and new-onset diabetes. Among patients in groups treated with more intensive management (defined as groups receiving the most potent pharmacological strategy at each trial), there was no significant association between 1 mmol/L reduction in LDL-C and new-onset diabetes incidence (risk ratio: 0.95; 95% CI, 0.87–1.04).[102] The same meta-analysis demonstrated that patients on PCSK9 inhibitor/statin combination treatment did not have a higher risk of developing diabetes.[102] Sub-studies with patients on PCSK9 inhibitors achieving very low (<30 mg/dL) LDL-C have shown no association with higher risk for developing diabetes.[16,18]

Cholesterol is a precursor of the five major classes of steroid hormones: progestogens, glucocorticoids, mineralocorticoids, androgens, and oestrogen.[103] However, there appears to be no significant effect on cholesterol based hormone levels or function in patients achieving very low LDL-C.[18]

Gastrointestinal system

In a sub-study of JUPITER, patients with LDL-C < 30 mg/dL had significantly higher incidence of hepatobiliary diseases (all causes), driven by increased rates of unspecified biliary diseases and cholelithiasis/choledocholithiasis. The median follow-up in JUPITER, however, was only 1.9 years. Of note, four other sub-studies in patients with very low LDL-C did not find any significant correlation between very low LDL-C and higher incidence of hepatobiliary conditions.[15,16,18,19]

Robinson *et al.*[18] showed that patients with LDL-C < 25 mg/dL treated with alirocumab do not have increased risk for developing hepatic steatosis, a complication commonly found in patients with familial hypobetalipoproteinemia.

Ocular system

In the HOPE-3 trial, individuals in the 10-mg rosuvastatin per day group had a statistically significant greater number of cataract surgeries than in the placebo group.[104] Pooled data from 14 alirocumab trials (though not including ODYSSEY OUTCOMES' data) showed that the rate of cataracts was higher in patients with LDL-C < 25 mg/dL (2.6%) vs. ≥25 mg/dL (0.8%; hazard ratio: 3.40; 95% CI: 1.58–7.35).[18] However, other sub-studies in patients with very low LDL-C did not find any significant correlation between very low LDL-C and cataract development.[15–17,19] These include results from the FOURIER trial with its large number of subjects with LDL-C < 20 mg/dL[16] and the IMPROVE-IT trial notable for its follow-up of over 6 years.[15] In ODYSSEY OUTCOMES, the cataract incidence for the alirocumab and the placebo groups was 1.3% vs. 1.4%, respectively, which also supports that dramatic LDL-C lowering does not increase cataracts.[7] Analysing ODYSSEY OUTCOMES' data of those patients who achieved very low LDL-C may further clarify whether there is a possible association between very low LDL-C and greater cataract risk.

Cancer

The SEAS study that investigated the effect of ezetimibe/simvastatin on major cardiovascular events in patients with asymptomatic aortic stenosis found slightly higher cancer (not specific type) rates in the treatment group, although not associated with the degree of LDL-C lowering.[105] However, an observational follow-up study of the SEAS treatment population demonstrated no increased cancer incidence in the 21-month period after completion of the original study (hazard ratio 0.55, 95% CI 0.27–1.11).[106] A univariate analysis of the long-term follow-up of the IMPROVE-IT study found the rate of new, worsening, or relapsing malignancies to be increase in patients from highest to lowest achieved LDL-C level, but this correlation was no longer statistically significant after adjusting for baseline variables.[15] A Mendelian randomization analysis showed lower LDL-C to be associated with higher risks of endometrial cancer of all histologies combined.[107]

The CTT meta-analysis that included multiple statin treatment trials did not find any correlation between statin therapy and any site-specific cancer or overall cancer incidence [relative risk (RR) 1.00, 95% CI 0.96–1.04].[11] There are no sub-studies where patients have attained very low LDL-C or sub-studies with long-term safety follow-up that have shown any association with higher cancer rates.[12,15–19]

Other systems

A sub-study of JUPITER found a higher rate of physician-reported haematuria in patients with LDL-C < 30 mg/dL.[17] However, the same sub-study did not show higher haematuria rates as determined by protocol-driven laboratory measurements. All other sub-studies in patients with very low LDL-C have shown no increase in haematuria incidence.[15,16,18,19]

Robinson *et al.*[18] using pooled data from 14 alirocumab trials showed that patients with LDL-C < 25 mg/dL had no significant difference in levels of gonadal hormones, or fat-soluble vitamins A, D, and K and had elevated vitamin E levels when adjusted for LDL-C values.

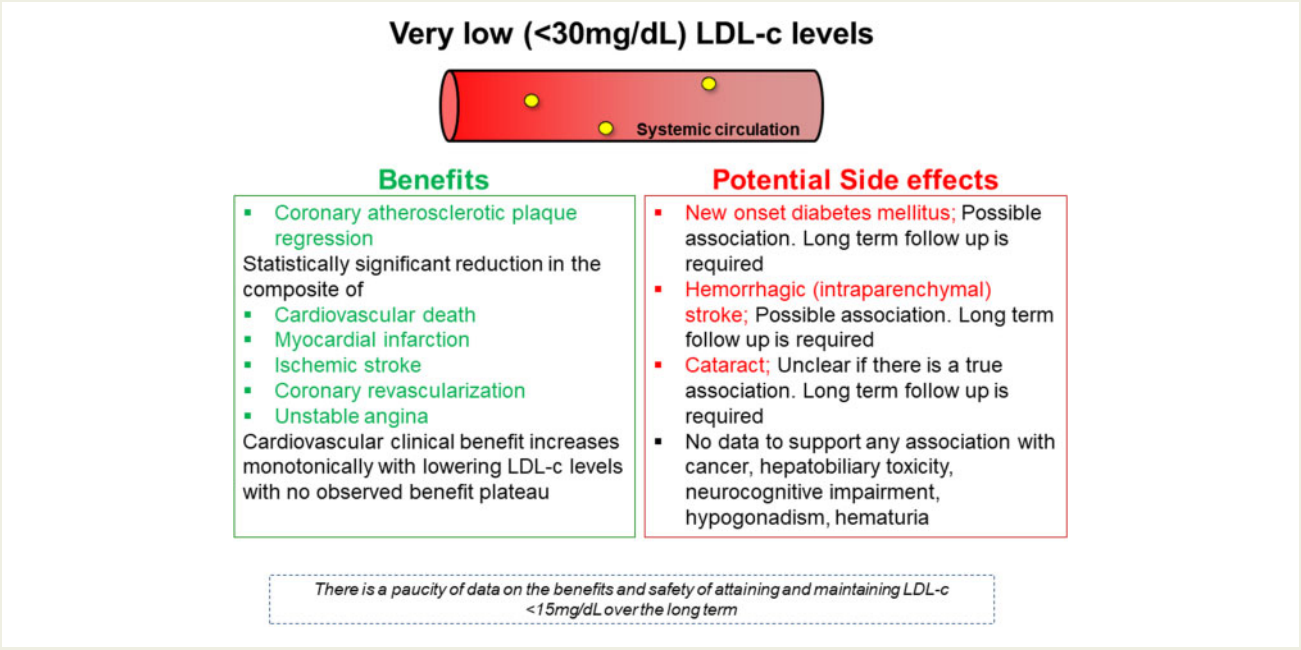


Figure 3 Benefits and potential side effects of very low (<30 mg/dL) LDL-C. An increasing number of patients are expected to attain very low LDL-C (<30 mg/dL) given the advent of potent lipid-lowering agents. The clinical impact of achieving very low LDL-C remains unclear. *Figure 3* summarizes potential benefits and side effects of attaining very low LDL-C.

Mortality

Few observational and prospective cohort studies that suffer from confounding have examined potential association of lower LDL-C levels with an overall mortality. Lower LDL-C and total cholesterol levels, in the elderly, not on lipid-lowering agents, Chinese, Finish, and Italian population, respectively, paralleled with higher mortality.[108–110] Patients with LDL-C < 77 mg/dL hospitalized for acute myocardial infarction had higher in-hospital mortality[111] and patients with LDL-C ≤ 21 mg/dL who were admitted with severe community-acquired pneumonia requiring intensive care unit hospitalization had decreased inpatient survival rate compared to control patients with higher LDL-C levels.[112]

Figure 3 summarizes all the potential benefits and side effects associated with very low LDL-C.

Discussion/conclusion

We reviewed genetic conditions associated with lifelong, very low LDL-C levels. Severe neurocognitive impairment and hepatic steatosis seen in abetalipoproteinemia and familial hypobetalipoproteinemia, respectively, are caused by mechanisms unrelated to very low LDL-C. Hundreds of healthy patients with PCKS9 loss-of-function mutations or familial combined hypolipidaemia living on lifelong low LDL-C for decades have been described.[55,57,113] On the contrary, individuals with *PCSK9* loss-of-function mutations appear to be healthy, without any evidence of neurocognitive impairment, higher incidence of diabetes, cataracts, or stroke.[48,113] These individuals experience significantly fewer coronary events compared to control groups and cardiovascular event rates are lower than expected based on patients' serum LDL-C.[9,47,113] This may be attributed to lifelong low LDL-C conferring more robust atheroprotection than attaining lower LDL-C later in life. Moreover, it may be enhanced by pleiotropic, LDL-C-independent, anti-atherosclerotic effects that have been associated with PCSK9 loss of function/inhibition.[114] Even though all aforementioned genetic conditions and lipid-lowering agents are associated with low LDL-C, the mechanism through which lower LDL-C is achieved differs (*Figure 4*). Increased LDL-C clearance thanks to LDL-R up-regulation appears to have fewer side effects compared to decreased lipoprotein secretion/lipoprotein toxic intracellular accumulation or decreased lipoprotein production.

We now possess the pharmacological armamentarium (statins, ezetimibe, PCSK9 inhibitors) to reduce LDL-C levels to an unprecedented extent. Recent guidelines for cholesterol management were updated to incorporate evolving evidence supporting the beneficial effects of aggressive LDL-C reduction[21,23] and it is likely a greater number of patients will achieve very low (<30 mg/dL) LDL-C. Clinicians, though, often feel uncomfortable encountering patients with very low LDL-C. Evidence to date supports the lack of significant correlation between very low LDL-C and major side effects. Whereas several studies have shown increased rate of diabetes, haemorrhagic stroke, haematuria, insomnia, hepatobiliary disorders, and cataract development among patients attaining very low LDL-C, the majority of studies have demonstrated no significant association. Whether this discrepancy is a result of confounders, selection bias, side effects related to a specific medication and not to lower LDL-C levels, inadequate sample sizes or insufficient Follow-up is yet to be clarified. Current data showing an overall safe profile of patient

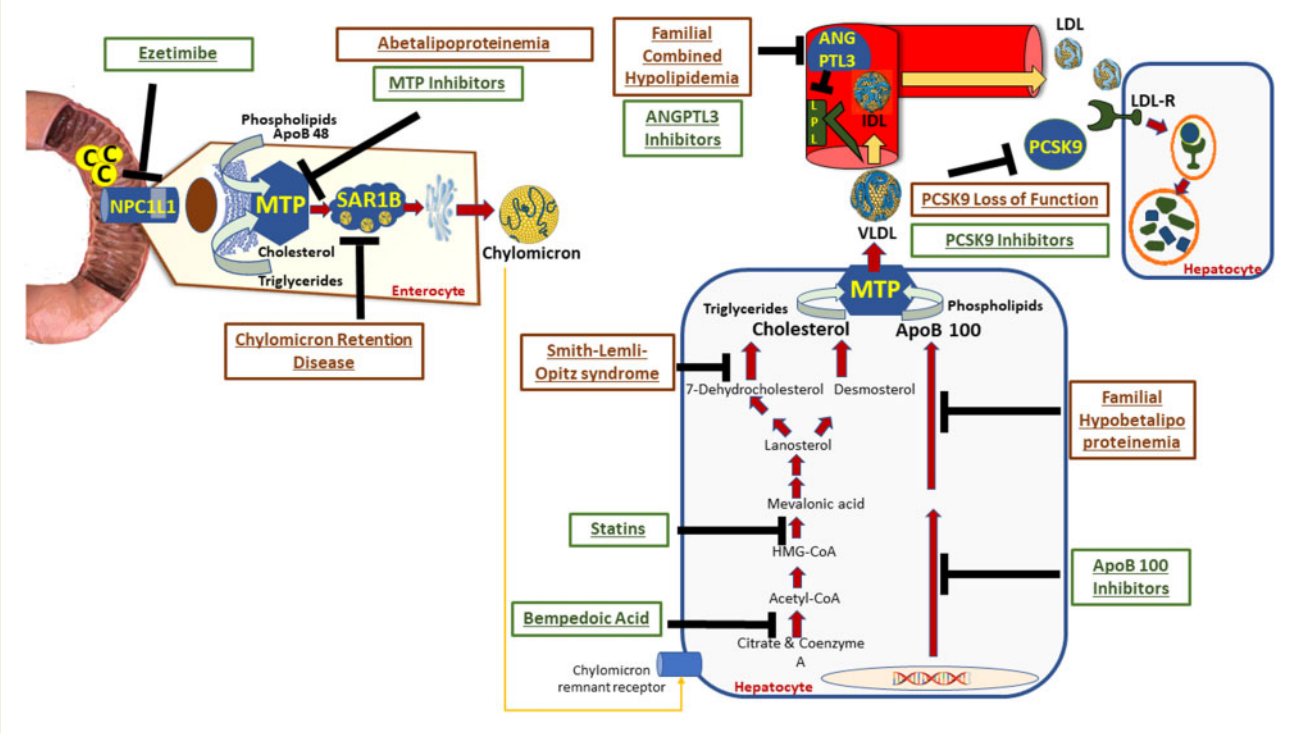


Figure 4 Overview of the molecular players of the LDL-C pathway. Several genetic conditions and lipid-lowering agents can all result in very low LDL-C via different though mechanisms. It is important to know the specific molecular players affected by each medication or genetic condition to predict and avoid potential side effects.

subgroups attaining very low LDL-C are post-randomization with therefore potential bias. Long-term exposure to very low LDL-C levels may be needed for real world statistical significance to become apparent. Observational studies and post marketing case reports would be useful to illuminate a possible association of very low LDL-C with a rare side effect in the long term. However, given inherent biases (due to non-blinding and non-randomization of patients) in observational studies, no causality can be inferred and, findings from non-randomized observational studies should be interpreted with caution and be further investigated in large-scale RCTs for confirmation.[11] Overall, a possible association of very low LDL-C with increased incidence of new-onset diabetes and haemorrhagic stroke necessitates further investigation.

Several new drugs have been approved or are under investigation for the management of hypercholesterolaemia and are anticipated to provide additional information on the safety of attaining very low LDL-C. Inclisiran, an siRNA PCSK9 inhibitor, has been shown to reduce LDL-C by 50% when administered subcutaneously every 6 months; lower LDL-C persists over an 18-month period, and 16% of patients receiving inclisiran attained LDL-C < 25 mg/dL (supplementary).[115] Furthermore, ORION-4 is an ongoing multicentre, double-blind, RCT with 15 000 patients, investigating the effect of inclisiran on reducing cardiovascular events.[116] Bempedoic acid, an inhibitor of ATP citrate lyase, is an oral anti-lipidemic agent that significantly reduces LDL-C when added to maximally tolerated statin therapy without observed muscle-related adverse effects but with associated higher hyperuricemia and gout risk.[117] CLEAR Outcomes is a randomized, double-blind, RCT with 14 000 participants to assess the effects of bempedoic acid on the occurrence of major cardiovascular events in patients who are statin intolerant.[118] An anti-ANGPTL3 antibody (evinacumab) and an antisense oligonucleotide targeting ANGPTL3-mRNA are currently undergoing clinical trials for the management of dyslipidaemias.[119,120] An MTP inhibitor (lomitapide) and an ApoB-100 mRNA inhibitor (mipomersen) significantly reduced LDL-C in patients with Homozygous Familial Hypocholesterolemia (HoFH) in phase III trials, but given MTP and ApoB-100 mRNA inhibitors have been shown to cause hepatotoxicity and hepatic steatosis, these drugs have been FDA approved only for managing patients with HoFH.[121–125] The recent development of several novel medications addressing hypercholesterolaemia based upon research related to populations with hypocholesterolaemia is a triumph of translational medicine.

An increasing number of patients will likely achieve LDL-C levels below 30 mg/dL, given the availability of efficient and safe lipid-lowering agents as well as the more aggressive primary and secondary prevention recommendations per updated guidelines. Evidence supports that cardiovascular clinical benefit increases monotonically in association with lowering LDL-C, without reaching any plateau even for LDL-C as low as 10 mg/dL. However, there is concern with the limited data regarding long-term safety of exposure to LDL-C < 15 mg/dL in RCTs (*Table 1*). Thus far, it remains unclear if the incremental benefit of reducing LDL-C below 30 mg/dL is significantly

advantageous to warrant the potential for increased complications and/or expenses. Moreover, cost-effectiveness, relative cardiovascular benefit and concomitant comorbidities (e.g. hypertriglyceridaemia) will need to be assessed before further reducing LDL-C to very low levels (<30 mg/dL) with an additional lipid-lowering agent vs. using a non-LDL-C-lowering intervention in patients at highest risk. The recent RCT results showing a significant reduction in ischaemic events in patients taking icosapent ethyl, especially in the subgroup of patients with ASCVD, triglycerides >135 mg/dL and LDL-C < 100 mg/dL, raises the question that lowering LDL-C to very low levels may not be the only option for all high-risk patients.[126] Given the potential for cardiovascular benefit and short-term safety profile of very low (≤30 mg/dL) LDL-C levels, it may be advantageous to attain such low levels in specific high-risk subsets of patients. Further studies are needed to compare the net clinical benefit of non-LDL-C-lowering interventions with aggressive LDL-C lowering, as well as to compare the efficacy and safety of attaining very low LDL-C levels vs. current recommended targets.

Data availability

The data underlying this article are available in the article.

Funding

A.M. is supported by AHA postdoctoral fellowship award 19POST34400057 and Abraham J & Phyllis Katz foundation.

Conflict of interest: none declared.

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